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47X 490 500 502 503
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624 625 628 62X 62Y
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668 672 680 682 697 699
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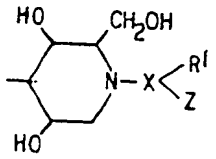
(54) Moranoline derivatives

(57) N-substituted moranoline derivatives of the formula



where X is alkylene, alkynylene or alkenylene, R^1 is H, phenyl or substituted phenyl, and Z is phenyl, substituted phenyl or thienyl are useful for treatment of hyperglycemia and related diseases.

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SPECIFICATION

Moranoline derivatives

Detailed description of the invention

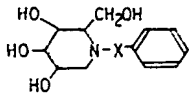
The present inventors previously isolated for the first time a substance represented by the formula (B) shown below as a naturally occurring substance from a Chinese medicine *Mori Cortex*, named the same "moranoline" and reported thereon (M. Yagi et al.; Nippon Nogeikagaku Kaishi, *50*, 571 (1976)).

Subsequent intensive investigation of the pharmacological activity of moranoline by the present inventors revealed that moranoline has a very useful activity for use as a drug, i.e. an activity of inhibiting blood sugar increase in sugar-loaded animals, this finding led them to an invention of a blood sugar increase inhibiting agent containing moranoline, and a patent application was filed (Japanese Kokai Sho-52 (1977)—83951).

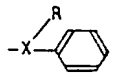
Thereafter, the present inventors have contunued extensive research works on various novel moranoline derivatives synthesized by them and found that certain N-aralkyl or N-aralkenyl derivatives of moranoline have far more potent blood sugar increase inhibiting activity as compared with moranoline, established methods of their synthesis, and completed this invention.

Now, for the convenience of understanding this invention only, we shall divide compounds of this invention into the following four categories. It should, however, be understood that it is for better understanding of this invention only and it never hinders the unity of this invention. They are as follows:

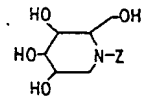
(A) N-substituted moranoline derivatives represented by the following general formula and acid addition salts thereof. In the formula, X represents a propylene or propenylene group.



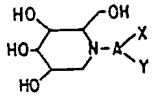
(B) An N-substituted moranoline derivative represented by the following general formula. In the formula, Z represents



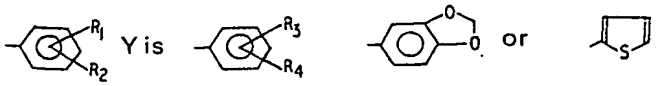
wherein R is hydrogen or phenyl, and X is alkylene or alkenylene containing 4 or 5 carbon atoms when R is hydrogen or X is alkenylene containing 3, 4 or 5 carbon atoms when R is phenyl.



(C) An N-substituted derivative of moranoline represented by the following general formula and acid addition salts thereof.

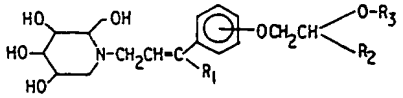


In the formula, A is hydrocarbon residue containing 3—6 carbon atoms and having or lacking a double bond, X is hydrogen, methyl or



wherein R_1, R_2, R_3 and R_4 are the same or different and each is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl, trihalomethyl, phenoxy, dialkylamino, cyano, carboxyl, carbomoyl or carboalkoxy,

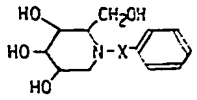
(D) A substituted cinnamyl-moranoline (following general formula) and acid addition salts thereof.



In the formula R_1 is hydrogen or methyl, R_2 is hrdrogen or hydroxymethyl and R_3 is hydrogen, methyl, ethyl or methoxyethyl.

Now this invention will be illustrated in the order of the above four categories.

(A) The first category compounds



When 10 mg/kg of a compound covered by the present category was administered orally to rats together with 2 g/kg of sucrose and the rate of blood sugar increase inhibition measured an hour later, the inhibition rate was 54% for the case where X was propenyl and as high as 93% for the case where X was propenylene. Thus it has been revealed that they have far more potent activity when compared with the inhibition rate of 28% shown by moranoline under the same test conditions.

As shown above, the compounds covered by the present category have potent blood sugar increase inhibiting activity, and are very useful as drugs for prophylaxis and treatment of hyperglycemic symptoms and various diseases caused by hyperglycemia, such as diabetes, prediabetes, hyperlipemia, arteriosclerosis, obesity, myocardial infarction and other heart diseases, gastritis, gastric ulcer, duodenal ulcer and other gastrointestinal diseases.

The substances are all novel compounds not yet described in the literature. The most common synthetic method therefor is the one starting from moranoline. Thus, they can be synthesized by reacting moranoline with a variety of active aralkylating or aralkenylating agents, typically aralkyl halides, aralkenyl halides, aralkyl sulfonates, aralkenyl sulfonates, etc., in a polar solvent such as water, an alcohol, DMSO, DMF, a cellosolve, a glyme or a mixture thereof, or in a suspension medium consisting of such a polar solvent and a nonpolar solvent such as benzene or hexane, in the presence of an appropriate deacidifying agent such as an alkali hydroxide, an alkali carbonate or an alkali hydrogen carbonate, at room temperature or under heating.

In cases where the reaction is carried out in a suspension medium, the reaction may be conducted in the presence of a phase transfer catalyst such as a cationic surfactant. A process may also be employed which comprises using as starting material a hydroxy-protected moranoline wherein the protective group is acetyl, benzoyl, tetrahydropyranyl or some other appropriate group, and removing the protective group after the N-substitution reaction. They can also be synthesized by such processes as the one comprising carrying out a so-called reductive N-alkylation reaction by using a reagent having a carbonyl group as reactant or the one comprising reducing an amide of moranoline with an aralkylcarboxylic acid or an aralkenylcarboxylic acid and recovering the contemplated compound.

The following examples will illustrate the invention.

EXAMPLE 1

Synthesis of N-phenylpropylmoranoline (XR^1Z=propenyl)

Moranoline (0.82 g) is dissolved in 2 ml of water and diluted with 6 ml of ehtanol, 1.3 g of phenylpropyl bromide and 0.38 g of potassium carbonate are added, and the mixture is heated at 80—90°C with stirring for 6 hours, then cooled, diluted with 100 ml of water, washed with ether and passed through an Amberlite (registered Trade Mark) IR—120B (H) ion exchange column. The adsorbate is eluted with 1% aqueous ammonia, the eluate evaporated to dryness under reduced pressure, the residue dissolved in isopropyl alcohol, 0.24 g of p-toluenesulfonic acid added, and the resulting crystalline precipitate collected by filtration. This is recrystallized from alcohol to give the contemplated compound. Yield 0.51 g. Melting point 219—221°C, $[\alpha]_D^{24} = -3.5°$ (water).

EXAMPLE 2

Synthesis of N-cinnamylmoranoline (XR^1=propenylene)

Moranoline (3.2 g) is dissolved in 100 ml of DMF, 7.9 g of cinnamyl bromide and 8.0 g of anhydrous potassium carbonate are added, and the mixture is heated at 70—80°C with stirring for 4 hours, then cooled, diluted with 400 ml of water, made acid with hydrochloric acid, and washed with benzene. The benzene layer is extracted with 1% hydrochloric acid, the combined aqueous layers are made alkaline with ammonia, and extracted with n-butanol. The extract is washed with water and evaporated to dryness under reduced pressure. The remaining crystals are recrystallized from methanol. Yield 2.8 g. Melting point 167—168°C. $[\alpha]_D^{24} = -49.0°$ (methanol).
The hydrochloride: recrystallized from methanol, m.p. 216—218°C. $[\alpha]_D^{24} = -15.0°$ (water).

(B) The second category compounds

Structurally, the novel moranoline derivatives covered by the present category can be characterized as N-aralkylmoranolines or N-aralkenylmoranolines. Their activity is far more potent than that of moranoline itself, as will be described later in detail. Moreover, among N-aralkylmoranolines, N-benzylmoranoline and N-phenethylmoranoline, which are structurally simpler than the compounds of the present category, are much weaker in activity than the N-aralkylmoranolines of the present category. Thus, only the substances covered by the present category, in other words those within the chain between the nitrogen atom of moranoline and the phenyl group contains 3 or more carbon atoms,

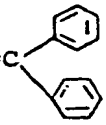
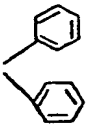
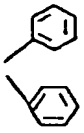
show a very strong activity. Whereas those N-aralkynylmoranoline derivatives that contain a triple bond between the nitrogen atom and the phenyl group, typically 3-phenyl-2-propynylmoranoline, 3-phenyl-2-butynylmoranoline, 4-phenyl-3-butynylmoranoline, 4-phenyl-3-pentynylmoranoline etc., have likewise a strong activity, their value in practice is small because of difficulty in their commercial production.

Further, there are some compounds that are similarly active among a group of substances which contain in place of the phenyl group residues of a variety of five- or six-membered, O-, N- and/or S-containing heterocyclic aromatic rings such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, pyridine, pyrimidine, pyridazine and pyrazine, or residues of those condensed rings that contain said heterocyclic aromatic rings. Nevertheless, although synthesis of said group of substances is indeed possible by methods analogous to those mentioned in this specification, generally the synthesis is very difficult and will never be acceptable from a commercial standpoint.

When the compounds covered by the present category are administered orally to rats at doses of 10 mg/kg with simultaneous administration of 2 g/kg of sucrose and the rate of inhibition of blood sugar increase is determined 60 minutes later, all of the compounds show approximately 100% or more inhibition. On the contrary, the inhibition rate for moranoline under the same test conditions was only 28%, and N-benzylmoranoline and N-phenethylmoranoline rather potentiated blood sugar increase by 35% and 21%, respectively.

In Table 1 are shown examples of the substances covered by the present category together with the rate of inhibition of blood sugar increase for them determined under the test conditions mentioned above.

Table 1

Compound No.	$X R^1 z$	% Inhibition
[I]	$-(CH_2)_4-$ 	127
[II]	$-(CH_2)_2-CH=CH-$ 	98
[III]	$-CH_2-CH=C(CH_3)-$ 	108
[IV]	$-CH_2-C(CH_3)=CH-$ 	90
[V]	$-CH_2-CH=C$ 	98
[VI]	$-(CH_2)_2-CH=C$ 	103
[VII]	$-(CH_2)_3-CH=C$ 	117
[VIII]	$-(CH_2)_5-$ 	94
[IX]	$-CH_2-(CH=CH)_2-$ 	117
[X]	$-(CH_2)_3-CH=CH-$ 	98
[XI]	$-(CH_2)_2-CH=C(CH_3)-$ 	95

As shown above, every substance covered by the present category has a potent blood sugar increase inhibiting activity, and is of course very useful as a drug for prophylaxis and treatment of hyperglycemic symptoms and various diseases caused by hyperglycemia in humans and animals, such as diabetes, arteriosclerosis, obesity, heart diseases, gastritis, gastric ulcer and duodenal ulcer, for instance.

The substances covered by the present category are all novel substances that have not yet been described in the literature, and can be synthesized e.g. by the following methods.

First of all, the commonest and most advantageous method is the one comprising N-alkylation of moranoline. Thus, they can be synthesized by reacting moranoline with a variety of aralkylating or aralkenylating agents in the presence of an appropriate deacidifying agent in a polar solvent such as water, an alcohol, DMSO, DMF, a cellosolve, a glyme or dioxane or a mixture thereof or in a suspension medium consisting of such polar solvent and a nonpolar solvent such as benzene or hexane. The active reagent include aralkyl halides, aralkenyl halides, aralkyl sulfonates and aralkenyl phosphates, for instance. The contemplated products can also be obtained by using as starting material an appropriately OH-protected moranoline and removing the protective group after the N-substitution reaction. Examples of said protective group are acetyl, benzoyl, benzyl and tetrahydropyranyl. It is also possible to

synthesize them by carrying out a so-called reductive alkylation or aralkenylation reaction using as reactant a carbonyl-containing reagent such as an aralkyl-aldehyde or aralkenyl-aldehyde. Various kinds of metal complex hydrides as well as catalytic hydrogenation can be employed as means of reduction in said case. The contemplated compounds can also be obtained by applying the method comprising said reductive alkylation or aralkenylation to nojirimycin or derivatives therof, thereby carrying out reduction and alkylation or aralkenylation simultaneously. Moreover, it is also possible to synthesize them e.g. by first synthesizing N-acylmoranoline derivatives and then reducing them to the corresponding N-alkyl or N-aralkenyl derivatives.

The following examples are examples of the substances covered by the present category together with a method of their synthesis and their physical properties.

Example 3 Synthesis of Compound I

Moranoline (3.26 g) is dissolved in a mixture of 25 ml of methanol and 25 ml of DMF with heating, 5.0 g of sodium bicarbonate and 8.5 g of 4-phenylbutyl bromide are added, and the mixture is heated and stirred at 80°C for 4 hours and then at 95°C for 2 hours. The reaction mixture is diluted with water, acidified by addition of hydrochloric acid, washed with benzene, made alkaline with ammonia and extracted with n-butanol. After washing with water, the butanol is distilled off. The remaining crystals are recrystallized from acetone. Melting point 118—119°C. Yield 2.91 g. $[\alpha]_D^{24} = -19.0°$ (methanol).

The p-toluenesulfonate salt: recrystallized from isopropyl alcohol. Melting point 163—164°C, $[\alpha]_D^{24} = -4°$ (water).

EXAMPLE 5 Synthesis of Compound II

Moranoline (3.26 g) is dissolved in 25 ml of DMF with heating, 4.0 g of sodium hydrogen carbonate and 7.0 g of 4-phenyl-3-butenyl bromide are added and the mixture is heated at 80—85°C with stirring for 6 hours.

The reaction mixture is treated as in Example 1, and 3.5 g of p-toluenesulfonic acid is added to the raction product so obtained to convert the same into the salt, which is recrystallized from ethanol. Melting point 160°—162°C, $[\alpha]_D^{24} = -8.0°$ (methanol). Yield 3.12 g.

EXAMPLE 6 Synthesis of Compound V

Moranoline (1.5 g) is dissolved in 20 ml of DMF with heating 1.5 g of potassium carbonate and 4.0 g of *p*-phenylcinnamyl bromide are added and the mixture is heated at 60° for an hour with stirring. Thereafter, the reaction product is recovered by the procedure of Example 1 and recrystallized from a mixture of ethyl acetate and n-hexane. Melting point 91°—94°C, $[\alpha]_D^{24} = -57.2°$ (methanol). Yield 0.93 g.

EXAMPLE 7 Synthesis of Compound XI

Moranoline (2.0 g) is dissolved in 40 ml of DMF with heating, 3.5 g of potassium carbonate and 5.5 g of 4-phenyl-3-pentenyl bromide are added and the mixture is heated at 60° for 11 hours with stirring. Thereafter, the reaction product is recovered by the procedure of Example 1 and recrystallized from isopropyl alcohol. Melting point 126°—131°C. $[\alpha]_D^{24} = -23.2°$ (methanol). Yield 0.40 g.

In the following are shown physical characteristics of other compounds covered by the present invention than those mentioned above. These have been synthesized according to the above process.

Compound III	Melting point: 169—170°C, $[\alpha]_D^{24} = -39.9°$ (methanol)
Compound IV	Melting point: 138—141°C, $[\alpha]_D^{24} = -71.4°$ (methanol)
Compound VI	Melting point: 164—166°C, $[\alpha]_D^{24} = -16.9°$ (methanol)
Compound VII	Melting point: 160—162°C, $[\alpha]_D^{24} = -10.4°$ (methanol)
Compound VIII	(p-toluenesulfonate) Melting point: 190—192°C, $[\alpha]_D^{24} = -2.7°$ (water)
Compound IX	Melting point: 116 — 118°C, $[\alpha]_D^{24} = -51.7°$ (methanol)
Compound X	(p-toluenesulfonate) Melting point: 223—226°C $[\alpha]_D^{24} = -4.6°$ (methanol)

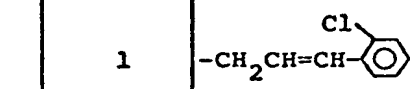
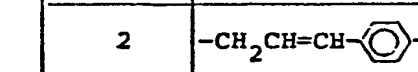
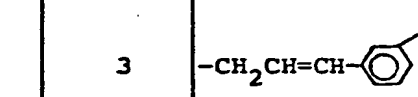
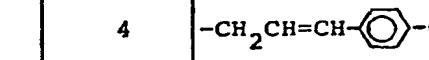
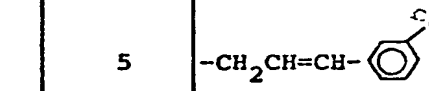
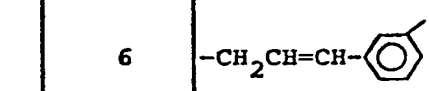
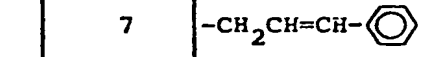
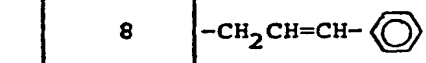
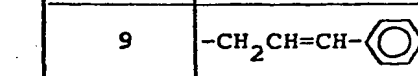
(C) The third category compounds

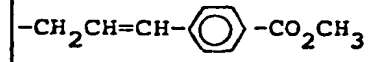
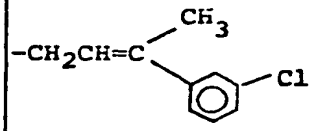
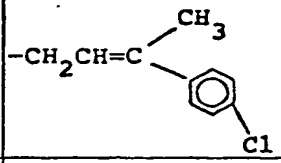
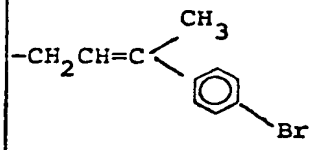
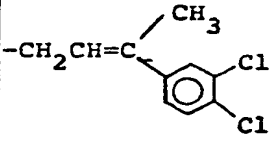
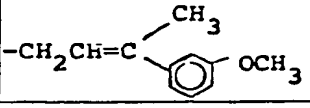
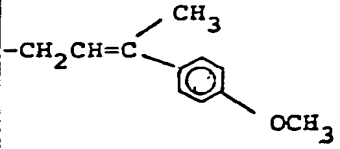
The compounds covered by the present category are characterized in that they are all N-(substituted alkyl)- or N-(substituted aralkenyl)-moranolines. Thus, they have a structure where the nitrogen atom has as substituent a hydrocarbon residue containing 3—6 carbon atoms, which residue has in turn on its carbon chain a phenyl, substituted phenyl or heterocyclic aromatic group.

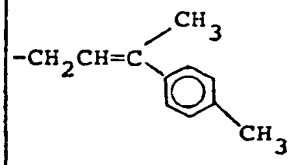
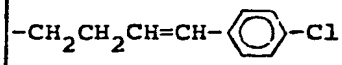
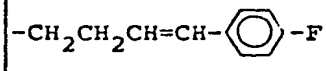
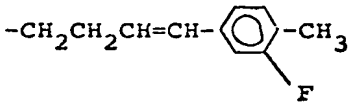
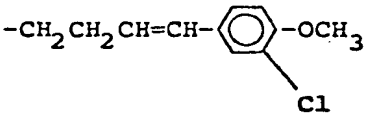
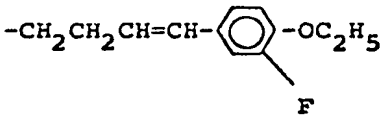
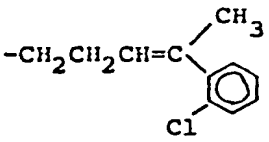
As will be seen from the data on a biological activity to be shown later, all the compounds covered by the present category have a far potent blood-sugar-increase inhibiting activity as compared with moranoline. Exceptionally, only a few compounds which are sparingly soluble in water are active only to approximately the same degree as moranoline. There also can be found some compounds that show similar activity as shown by the compounds of the present invention among compounds which have the same carbon skeleton as that of the compounds of the present invention and contain a triple bond as an unsaturated bond in the carbon chain and among compounds which have aromatic rings other than the phenyl or thiophene ring, such as naphthyl, O-, N- or S-containing five- or six-membered, heterocyclic aromatic groups, e.g. furan, pyrrole, imidazole, pyrazole, oxazole, thiazole, pyridine, pyrimidine, pyridazine and pyrazine residue, or condensed ring groups comprising said heterocyclic groups, e.g. benzofuran, indole, benzothiophene, quinoline and purine residue. Also, some effective substances can be found among compounds wherein said condensed ring has been converted to such a skeleton as carbostyril, isocarbostyril, indane, coumarine, isocoumarine and benzopyrone. Thus, it seems that the blood sugar increase inhibiting activity possessed by the compounds covered by the present category is an activity generally recognizable in the group of compounds similar in structure to the compounds of the present invention, without being essentially influenced by certain changes in the kind of aromatic ring, kind of the substituent on the aromatic ring, structure of the hydrocarbon residue, etc. Nevertheless, the number of carbon atoms in the hydrocarbon residue and especially the number of carbon atoms in the main chain which is determinant of the distance between the nitrogen atom of moranoline and the aromatic have great influence upon the activity. If the chain length is beyond the limits, specified by the present category, i.e. 3—5 carbon atoms, the activity will be much lower and some compounds will even potentiate blood sugar increase.

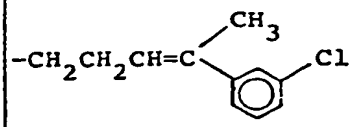
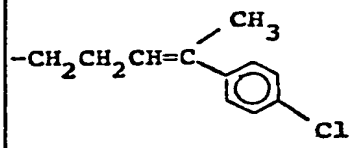
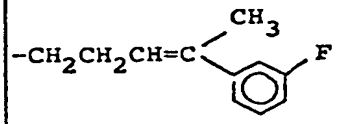
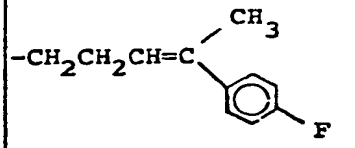
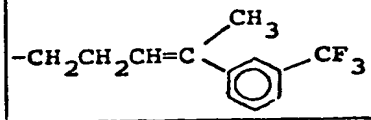
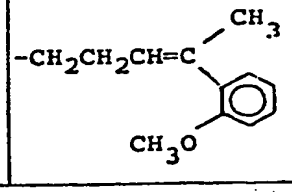
When the compounds of the category are administered to rats orally at a dose of 10 mg/kg together with 2 g/kg of sucrose and the rate of inhibition of blood sugar increase is measured 60 minutes after administration, most of the compounds show inhibition rates higher than 70%. Those compounds which show exceptionally low inhibition rates of 20—30% are all very poor in water solubility, which fact appears to be one of the causes of the low activity found in that experiment. Even these compounds which show relatively low activity are almost equally or more active than moranoline itself which shows an inhibition rate of 28% under the same test conditions. Two examples of those compounds which are outside the scop of the category and have carbopn chains beyond the limits of 3—5, namely N-phenylmoranoline and N-benzylmoranoline potentiated blood sugar increase by 21% and 35%, respectively, and another example of such compounds, N-(8-phenyloctyl)moranoine showed a very low activity, that is an inhibition rate of 11%.

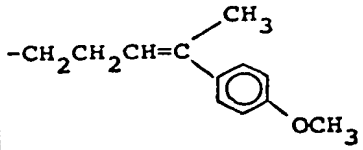
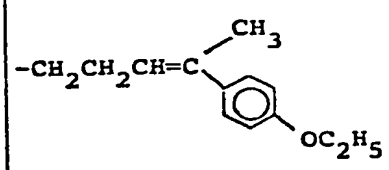
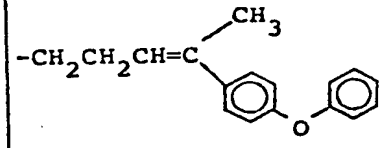
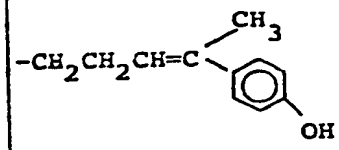
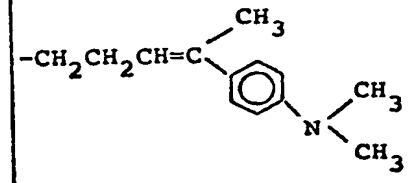
Table 2

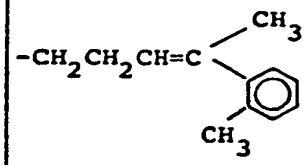
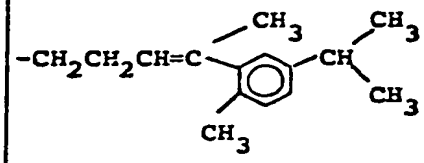
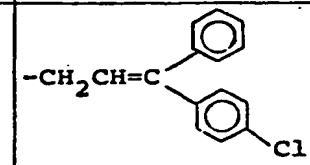
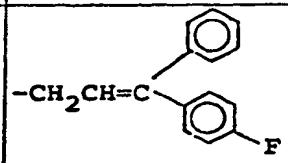
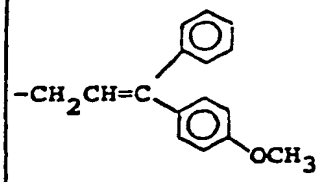
Compound No.	$-X<_{Z}^{R^1}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
1		122	117-179	-29.3° (methanol)
2		72	225-228	-43.6° (methanol)
3		118	167-169	-50.1° (methanol)
4		100	181-184	-48.9° (methanol)
5		107	157-160	-45.7° (methanol)
6		98	187-190	-49.6° (methanol)
7		108	171-172	-50.9° (methanol)
8		100	hydrochloride 258-262 (decomposition)	-17.8 (water)
9		102	218-220	-3.7° (acetic acid)

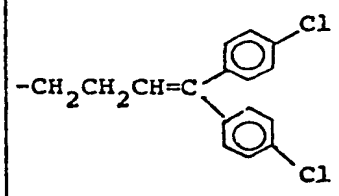
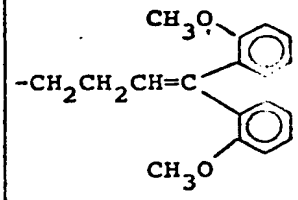
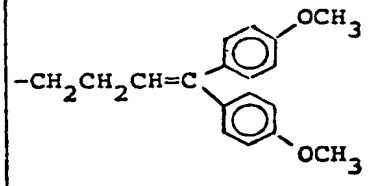
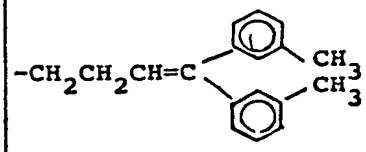
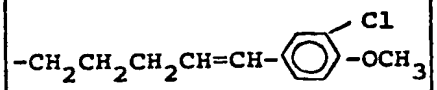
Compound No.	$-X<^{R^1}_{Z}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
10		97	hydrochloride 197-199	-12.3° (methanol)
11		100	145-147	-41.6° (methanol)
12		127	174-175	-43.7° (methanol)
13		99	184-186	-32.0° (methanol)
14		100	162-164	-37.6° (methanol)
15		113	159-161	-39.6° (methanol)
16		105	177-179	-60.8° (methanol)

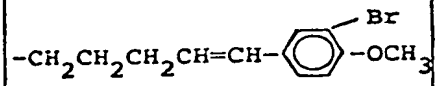
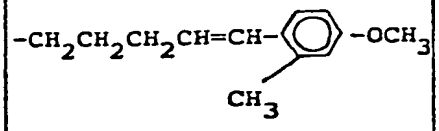
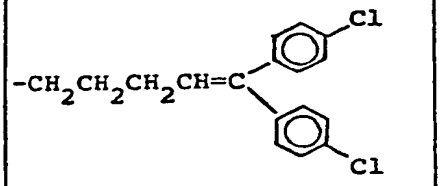
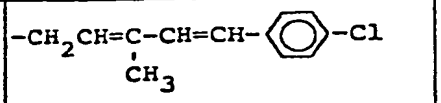
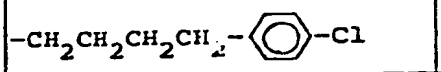
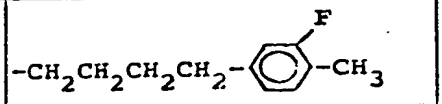
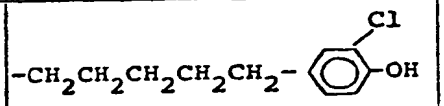
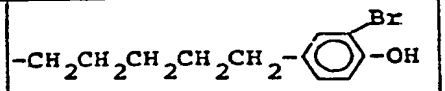
Compound No.	$-X\langle_{Z}^{R^1}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
17		111	166-169	-45.6° (methanol)
18		70	162-165	-25.8° (methanol)
19		65	168-172	-23.8° (methanol)
20		78	161-163	-22.7° (methanol)
21		84	173-175	-20.2° (methanol)
22		89	189-193	-21.3° (DMSO)
23		51	hydrate 72 - 76	-13.4° (methanol)

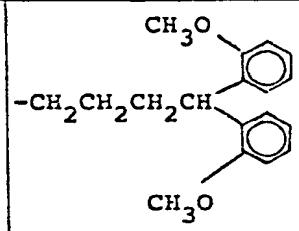
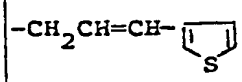
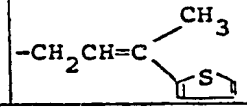
Compound No.	$-X\langle_{Z}^{R^1}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
24		73	129-133	-22.8° (methanol)
25		80	160-163	-24.7° (methanol)
26		106	146-150	-24.0° (methanol)
27		93	145-148	-21.7° (methanol)
28		36	140-144	-22.7° (methanol)
29		83	hydrate 56 - 60	-13.9° (methanol)

Compound No.	$-X\langle_{Z}^{R^1}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
30		102	152–156	-32.8° (ethanol)
31		109	147–151	-18.6° (methanol)
32		75	hydrate 85 - 90	-17.2° (methanol)
33		77	169–173	-18.8° (methanol)
34		103	176–181	-26.2° (methanol)

Compound No.	-X<Z R1	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
35		73	124-127	-19.7° (methanol)
36		54	hydrate 48 - 52	-16.4° (methanol)
37		30	hydrate 99-100	-59.5° (methanol)
38		22	145-147	-58.5° (methanol)
39		70	amorphous powder	-44.3° (methanol)

Compound No.	$-X<^{R^1}_{Z}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
40		50	ethylene glycol adduct 102-105	-11.7° (methanol)
41		68	167-169	-9.6° (methanol)
42		75	hydrate 90 - 94	-19.0° (DMSO)
43		45	hydrate 78 - 80	-14.5° (methanol)
44		94	111-115	-14.6° (methanol)

Compound No.	$-X<^{R^1}_{Z}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
45		84	115-117	-17.3° (methanol)
46		97	hydrate 71 - 74	-12.1° (methanol)
47		24	127-130	-13.6° (methanol)
48-		85	180-183	-27.2° (pyridine)
49		101	128-130	-18.0° (methanol)
50		114	125-127	-17.0° (methanol)
51		78	hydrate 70 - 75	-13.1° (methanol)
52		72	143-146	-10.8° (methanol)

Compound No.	$-X<^{R^1}_{Z}$	% Inhibition	m.p. (°C)	$[\alpha]_D^{24}$
53		107	184-186	-15.1° (DMSO)
54		99	159-162	-57.5° (methanol)
55		101	181-183	-55.3° (methanol)

As shown above, the substances covered by the present category all have potent blood sugar increase inhibiting activity, and of course are very useful as drugs for the treatment and prophylaxis of hyperglycemic symptoms and various diseases caused by hyperglycemia in human and animals, such as diabetes, arteriosclerosis, obesity, heart diseases, gastritis, gastric ulcer, duodenal ulcer, etc.

All the substances covered by the invention are novel substances that have not yet been described in the literature, and can be synthesized by the following methods, for instance.

The commonest and most advantageous method is N-alkylation of moranoline. Thus, they can be synthesized by reacting moranoline with a variety of active aralkylating or aralkenylating agent in the presence of an appropriate deacidifying agent in a polar solvent such as water, an alcohol, DMSO, DMF, a cellosolve, a glyme or dioxane or a mixture thereof or a suspension medium consisting of such polar solvent and a nonpolar solvent such as benzene or hexane. Examples of the active reagent are aralkyl halides, aralkenyl halides, aralkyl sulfonate and aralkenyl phosphates. It is also possible to obtain the contemplated products by using an OH-protected moranoline as a starting material and removing the protective group after the N-susbtitution reaction. Acetyl, benzoyl, benzyl and tetrahydropyranyl, for example, are suitable protective groups. Further, they can be synthesized also by a so-called reductive alkylation or aralkenylation using as a reagent a carbonyl-containing agent such as an aralkyl- or aralkenylaldehyde. In this case, various kinds of metal complex hydrides as well as catalytic hydrogenation may be employed as means of reduction. The contemplated products can also be obtained by applying said reductive alkylation or aralkenylation to nojirimycin or derivatives thereof and thereby accomplishing the reduction and alkylation or aralkenylation simultaneously. They can also be synthesized by first preparing N-acylmoranoline derivatives and then reducing the same to N-alkyl or N-aralkenyl derivatives, or by some other methods. Moreover, it is possible to derive those compounds that have such a substituent as carboxyl, carbamoyl or carboalkoxy on the aromatic ring from the corresponding nitrile group-containing compounds, e.g. Compound 7, by hydrolysis. In addition it is possible to convert one of the compounds just mentioned into another one just mentioned, and vice versa. Further, a hydroxyl-containing compound can be converted into the corresponding alkoxy-containing compound and vice versa, as in the case of Compound 30 and Compound 33.

The following examples describe typical examples of the compounds covered by the present category together with a method of production thereof shown by way of example. All the compounds falling within the scope of the present category can be synthesized by the same method as or a method analogous to that described in the Examples.

EXAMPLE 8 Synthesis of Compound 5

m-Methylcinnamyl bromide (2.0 g) (obtained by treatment with concentrated hydrobromic acid of 1-(m-methylphenyl) allyl alcohol prepared in turn from m-methylbenzaldehyde and vinyl magnesium bromide), 1.0 g of moranoline and 3.0 g of sodium hydrogen carbonate are stirred in 15 ml of ethylene glycol at 40—55°C for 1.5 hours. After completion of the reaction, the reaction mixture is diluted with 100 ml of water, and acidified with hydrochloric acid. The neutral substance is removed by extraction with ether. The aqueous layer is made alkaline with ammonia and extracted with n-butanol. The extract is purified by silica gel column chromatography using chloroform-methanol (3:1), and recrystallized from isopropyl alcohol. Yield 0.65 g. Melting point 157—160°C. $[\alpha]_D^{24} = -45.7°$ (methanol).

EXAMPLE 9 Synthesis of Compounds 8 and 9

Compound 7 (0.5 g) prepared in the same manner as for Compound 5 (Example 8) is allowed to stand in 30 ml of concentrated hydrochloric acid at room temperature overnight. The reaction mixture is evaporated to dryness under reduced pressure, and the residue dissolved in 5 ml of water and the solution made alkaline with ammonia. The resulting crystalline precipitate is recrystallized from aqueous methanol. Yield 0.29 g. Melting point 218—220°C. $[\alpha]_D^{24} = -3.7°$ (acetic acid).

Compound 7 (1.8 g) is heated in 70 ml of concentrated hydrochloric acid at 95°—100° for 3 hours, and the reaction mixture concentrated to about 20 ml under reduced pressure. The precipitate which forms on cooling is collected by filtration and recrystallized from methanol. Yield 1.42 g. Melting point 258—262°C (decomposition). $[\alpha]_D^{24} = -17.8°$ (water).

EXAMPLE 10 Synthesis of Compound 12

The crude reaction product obtained by stirring 5.0 g of the carbinol compound (prepared from p-chloroacetophone and vinyl magnesium bromide with 30 ml of concentrated hydrobromic acid for an hour is stirred with 1.5 g of moranoline and 4.0 g of sodium hydrogen carbonate in 15 ml of ethylene glycol at 60—70°C for 2 hours. The same treatment as in Example 8 followed by recrystallization of the reaction product from isopropyl alcohol gives a yield of 1.1 g. Melting point 174—175°C. $[\alpha]_D^{24} = -43.7°$ (methanol).

EXAMPLE 11 Synthesis of Compound 21

4-(3-Chloro-4-methoxyphenyl)-3-butenyl bromide is prepared by stirring 4.0 g of 1-(3-chloro-4-methoxyphenyl)-1, 3-butanediol (obtainable from o-chloroanisole and succinic anhydride by Friedel-Craft reaction followed by esterification and reduction with lithium aluminium hydride) and 4.0 g of phosphorus tribromide in 40 ml of benzene at 0—5°C for 5 hours followed by stirring at room temperature for 12 hours. The bromide (2.7 g), 1.3 g of moranoline and 4.5 g of potassium carbonate are stirred in 50 ml of DMF at 70—80°C for 14 hours. The reaction product recovered by the procedure of Example 8 is recrystallized from methanol. Yield 0.6 g. Melting point 173—175°C. $[\alpha]_D^{24} = -20.2°$ (methanol).

EXAMPLE 12 Synthesis of Compounds 30 and 33

The carbinol compound (14 g) obtained by Grignard reaction of cyclopropyl methyl ketone and p-methoxy magnesium bromide is stirred with 40 ml of concentrated hydrobromic acid at room temperature for an hour, and the reaction product stirred together with 3.0 g of moranoline and 15 g of potassium carbonate in 80 ml of DMF at 60—70°C for 5 hours. The reaction product recovered by the procedure of Example 1 is recrystallized from isopropyl alcohol. Yield 1.9 g. Melting point 152—156°C. $[\alpha]_D^{24} = -32.8°$ (ethanol).

Compound 30 (0.7 g) is heated with 10 g of pyridine hydrochloride at 200°C for 30 minutes. The reaction product is recovered by the procedure of Example 1 and recrystallized from isopropyl alcohol. Yield 0.35 g. Melting point 169—173°C. $[\alpha]_D^{24} = -18.8°$ (methanol).

EXAMPLE 13 Synthesis of Compound 38

The carbinol compound (5.0 g) prepared from 4-flourobenzophenone and vinyl magnesium bromide by Grignard reaction is stirred with 25 ml of concentrated hydrobromic acid at room temperature for an hour. The reaction product together with 1.5 g of moranoline and 5.0 g of sodium hydrogen carbonate is stirred in 15 ml of ethylene glycol at 60—70°C for 6 hours. The reaction product is recovered by the procedure of Example 1 and recrystallized from ethyl acetate. Yield 1.75 g. Melting point 145—147°C. $[\alpha]_D^{24} = -58.5°$ (methanol).

EXAMPLE 14 Synthesis of Compound 41

The carbinol compound (13 g) prepared from ethyl cyclopropane carboxylate and o-methoxyphenyl magnesium bromide is stirred with 50 ml of concentrated hydrobromic acid at room temperature for 2 hours. The reaction product obtained (10 g) is stirred with 2.5 g of moranoline and 6.0 g of potassium carbonate in 60 ml of DMF at 65° for 14 hours. The reaction product is recovered by the procedure of Example 1 and recrystallized from isopropyl alcohol. Yield 4.1 g. Melting point 167—169°C. $[\alpha]_D^{24} = -9.6°$ (methanol).

EXAMPLE 15 Synthesis of Compound 44

1-(3-Chloro-4-methoxyphenyl)-1,5-pentanediol synthesized from o-chloroanisole and glutaric anhydride by the same procedure as employed for Compound 21 is reacted with triphenylphosphine and carbon tetrabromide in acetonitrile. The resulting bromine derivative (6.0 g) is stirred with 1.0 g of moranoline and 5.0 g of potassium carbonate in 30 ml of ethylene glycol at 60—70° for 5 hours. The reaction product is recovered by the procedure of Example 1 and recrystallized from water. Yield 0.50 g. Melting point 111—115°C. $[\alpha]_D^{24} = -14.6°$.

Example 16 Synthesis of compound 47

The reaction product obtained by refluxing with 30 ml of concentrated hydrobromic acid for an hour 5.0 g of the carbinol compound prepared from δ-valerolactone and p-chlorophenyl magnesium bromide is stirred with 1.0 g of moranoline and 5.0 g of sodium hydrogen carbonate in a mixture of 10 ml of ethylene glycol and 10 ml of DMF at 85°C for 4.5 hours. The reaction product is recovered by the procedure of Example 8 and recrystallized from isopropyl alcohol. Yield 0.26 g. Melting point 127—130°C. $[\alpha]_D^{24} = -13.6°$ (methanol).

EXAMPLE 17 Synthesis of Compound 48

The carbinol compound (5.0 g) prepared from p-chloro-benzalacetone and vinyl magnesium bromide is stirred with 25 ml of concentrated hydrobromic acid at 3—5°C for 45 minutes, and the reaction product stirred with 1.0 g of moranoline and 5.0 g of sodium hydrogen carbonate in 10 ml of ethylene glycol at 60—70°C for 2 hours. The reaction product is recovered by the procedure of Example 1 and recrystallized from ethanol. Yield 0.35 g. Melting point 180—183°C. $[\alpha]_D^{24} = -27.2°$ (pyridine).

EXAMPLE 18 Synthesis of Compound 54

The carbinol compound (5.0 g) prepared from thiophene-2-aldehyde and vinyl magnesium bromide is dissolved in 50 ml of chloroform, 4.1 g of moranoline added, and 3.6 g of methanesulfonyl chloride dropped over 10 minutes with ice cooling. After stirring at 0—10°C for 0.5 hour, the reaction mixture is washed with water and dried, and the solvent distilled off under reduced pressure. The remaining reaction product is stirred with 1.0 g of moranoline and 5.0 g of sodium hydrogen carbonate in 10 ml of ethylene glycol at 55—65°C for 2 hours. The reaction product is recovered by the procedure of Example 8 and recrystallized from isopropyl alcohol. Yield 0.15 g. Melting point 159—162°C. $[\alpha]_D^{24} = -57.5°$ (methanol).

(D) The fourth category compounds

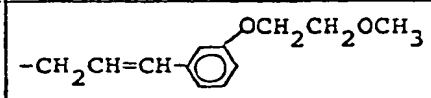
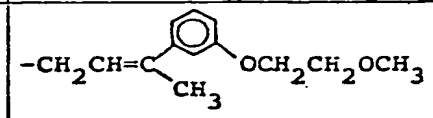
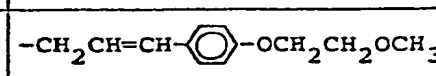
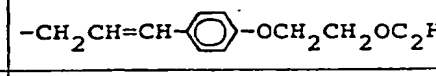
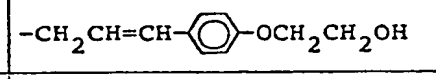
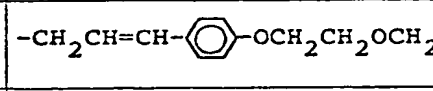
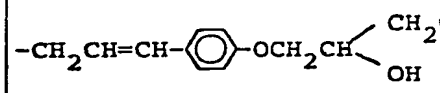
All the compounds covered by the present category are novel compounds, and can be regarded structurally as N-cinnamylmoranoline derivatives. The blood sugar increase inhibiting activity of a variety of N-aralkyl or aralkenyl derivatives of moranoline is much dependent on the number of carbon atoms contained in the carbon chain between the aromatic ring and the nitrogen atom of moranoline. When the chain is of 1 or 2 carbon atoms, no activity can be found at all, but only when the chain contains 3 or more carbon atoms, the activity is found. Especially when the chain contains 3 or 4 carbon atoms, the activity is maximal, and particularly the activity of N-cinnamylmoranoline is very strong.

Further, those derivatives that have a substituent at the p-position of the cinnamyl group, such as α methylcinnamyl and p-ethylcinnamyl derivatives, are as active as the cinnamyl derivative. Generally, those derivatives that have as substituent a variety of alkoxy groups on the aromatic nucleus are highly active. Among others, the compounds having a glycol ether type substituent and covered by the present invention are highly active and of low toxicity, and especially useful as drugs. The cinnamyl derivatives having said glycol ether type substituent include, in addition to the substances covered by the present invention, those cinnamyl derivatives that have an ethoxy or propoxy group substituted by a variety of alkoxy groups of 1 to 18 carbon atoms. They may have two or more of said glycol ether type substituents, and of course there may be present a number of isomers depending on the position of substitution. The useful physiological activity possessed by the substances covered by the present invention is a property common to said glycol ether type cinnamylmoranoline derivatives in general, but not limited to the substances covered by the present invention.

All of the substituted cinnamylmoranoline derivatives covered by the present category not only have very potent activity as compared with moranoline but also have much more potent activity than N-alkylmoranolines or unsubstituted cinnamylmoranolines.

In Table 3, the activity of typical examples of the substances covered by the present category is compared with that of N-benzylmoranoline, N-phenethylmoranoline, N-cinnamylmoranoline as well as moranoline and N-methylmoranoline. The activity is shown in terms of % inhibition obtained by comparing the blood sugar increase 120 minutes after the oral administration of 1 mg/kg of the test substance together with 2 g/kg of sucrose to rats with that found in the control group.

Table 3

Compound No.	$-X<^{R^1}_{Z}$	Inhitition rate
1		128%
2		106%
3		80%
4		93%
5		90%
6		126%
7		91%
Moranoline	H	41%
N-Methylmoranoline	$-CH_3$	33%
N-Benzylmoranoline	$-CH_2-\bigcirc$	-12.1%
N-Phenethylmoranoline	$-CH_2CH_2-\bigcirc$	-3.6%
N-Cinnamylmoranoline	$-CH_2CH=CH-\bigcirc$	51%

As shown above, every substance covered by the present category has a potent blood sugar increase inhibiting activity, and is of course very useful as a drug for prophylaxis and treatment of hyperglycemic symptoms and various diseases caused by hyperglycemia in humans and animals, such as diabetes, arteriosclerosis, obesity, gastritis, gastric ulcer and duodenal ulcer, for instance.

The substances covered by the present category are all N-substituted cinnamyl derivatives, and can be synthesized by various synthetic methods generally applicable to N-aralkenylation of amines. Thus, a method utilizing a common nucleophilic substitution reaction using an active, substituted cinnamyl group-containing compound such as a substituted cinnamyl halide, sulfonate or phosphate, or a so-called reductive alkylation using a substituted cinnamaldehyde is practicable generally with advantage. The contemplated products can also be synthesized by a process comprising preparation of amide compounds with cinnamic acid etc. followed by reduction of the carbonyl group. As one of the starting materials for these reactions there may of course be used moranoline itself, but the contemplated compounds can be obtained also be using as intermediate an appropriately OH-protected moranoline and removing the protective group after the N-substitution reaction, said protective group being acetyl, benzoyl, benzyl or tetrahydropyranyl, for instance. Those compounds whose substituent on the aromatic ring has one or more hydroxyl groups, typically Compounds 5 and 7, may be synthesized by first synthesizing an intermediate having a phenolic hydroxyl group and then reacting this with an epoxy reagent such as ethylene oxide or glycidol in alkaline conditions as well as by using the synthetic methods mentioned above.

The following examples illustrate one of the synthetic methods for typical compounds falling within the scope of the present category.

Example 19 Synthesis of compound 1

A solution of 12.7 g of m-β-methoxyethoxybenzaldehyde (prepared by reaction of m-hydroxybenzaldehyde with methoxy-ethyl bromide in DMF in the presence of anhydrous potassium carbonate) in 50 ml of anhydrous tetrahydrofuran is dropped into an anhydrous tetrahydrofuran solution containing about 22 g of vinyl magnesium bromide with stirring and ice cooling. After the dropping stirring is continued at room temperature for 30 minutes, and thereafter the mixture is treated in a usual manner to give 12.6 g of the carbinol type compound as a colorless oil.

The so-obtained carbinol (12 g) is dissolved in 50 ml of ether, thereto is added 8.1 g of phosphorus tribromide with ice cooling, and stirring is made for 5 minutes. The reaction mixture was washed with 100 ml of cold water, the ether layer dried over anhydrous magnesium sulfate, and the ether distilled off at below 30°C under reduced pressure. There is obtained 14 g of the cinnamyl bromide derivative as a pale yellow oil.

On the other hand, 3.0 g of moranoline is dissolved in 50 ml of ethylene glycol, 5.0 g of sodium bicarbonate then added, further the above cinnamyl bromide derivative added with stirring at room temperature over about 20 minutes, and the mixture stirred at room temperature for 3 hours. Thereafter the reaction mixture is diluted with water, acidified with hydrochloride acid, washed with ether, made alkaline with ammonia, and extracted with n-butanol. The butanol is distilled off, and the remaining crystalline substance recrystallized from a mixture of isopropyl alcohol and methanol.

Yield 4.1 g. Melting point 136—138°C. $[\alpha]_D^{24}=-39.7°$ (methanol)

EXAMPLE 20 Synthesis of Compound 2

m-β-Methoxyethoxyacetophenone prepared from m-hydroxy-acetophone and methoxyethyl bromide is subjected to Grignard reaction as in Example 19, and the resulting carbinol compound (14.3 g) treated in 50 ml of ether with 9.2 g of phosphorus tribromide with ice cooling for 5 minutes, to give 16.4 g of the cinnamyl bromide type compound. Moranoline (3.1 g) is dissolved in 50 ml of DMSO, 5.0 g of sodium bicarbonate added, and 16 g of the bromide obtained above dropped with stirring at room temperature over 1.5 hours. After the dropping, stirring is continued for 30 minutes. Thereafter the same treatment procedure as in Example 1 follows, and the butanol extract treated with isopropyl alcohol. The resulting crystals are recrystallized from ethanol. Yield 3.13 g. Melting point 116—119°C. $[\alpha]_D^{24}=-34.9°$ (methanol).

EXAMPLE 21 Synthesis of Compound 3

Using p-hydroxybenzaldehyde as starting material and proceeding as in Example 19, there is obtained 7.1 g of the bromide, which is reacted with 3.2 g of moranoline and 3.3 g of sodium bicarbonate in 30 ml of DMSO with stirring at room temperature for an hour. Thereafter the reaction mixture is treated as in Example 19, and the butanol extract obtained is recrystallized from ethanol. Yield 1.68 g. Melting point 172—174°C. $[\alpha]_D^{24}=-48.6°$ (methanol).

Compounds 4 and 6 were prepared in the same manner as in Examples 19, 20 and 21.

Compound 4	Melting point 166—169°C $[\alpha]_D^{24}=-43.1°$ (methanol)
Compound 6	Melting point 118—121° $[\alpha]_D^{24}=-37.7°$ (methanol)

EXAMPLE 22 Synthesis of Compounds 5 and 7

p-Hydroxybenzaldehyde (20 g) is dissolved in 200 ml of DMF, 44 g of anhydrous potassium carbonate and 45 g of β-methoxyethoxymethyl chloride are added, and the mixture is stirred at room temperature for 3 hours. Dilution with water, ether extraction and distillation of the extract under reduced pressure give 25 g of a fraction having b.p. 150—153°C/5 mmHg. This is subjected to Grignard reaction with vinyl magnesium bromide as in Example 19, 20 or 21, the carbinol so obtained treated in ether with an equimolar amount of thionyl chloride at −10°C for one minute, and the resulting cinnamyl chloride type compound reacted with moranoline in DMSO in the presence of sodium bicarbonate as in Example 2 or 3, giving p-β-methoxyethoxymethoxycinnamylmoranoline. Melting point 111—114°C.

The crystals (5.2 g) obtained above is dissolved in 50 ml of methanol, 2 ml of concentrated hydrochloric acid and 5 ml of water are added, and the mixture is refluxed for 2.5 hours. The reaction mixture is evaporated to dryness under reduced pressure, the residue washed with ether, and the insoluble matter treated with a mixture of ethanol and ethyl acetate to cause crystallization. Yield 3.1 g (p-hydroxycinnamyl-moranoline hydrochloride).

Synthesis of Compound 5

The crude crystals (1.0 g) obtained above is dissolved in 30 ml of methanol containing 1.0 g of potassium hydroxide, 2 ml of ethylene oxide added, and the mixture heated in a sealed tube at 80°C for 3 hours. The reaction mixture is evaporated to dryness under reduced pressure, and the residue

dissolved in water and passed through a Dowex 50W x 4 (H form) ion exchanger column. The column is washed with water, the adsorbate eluted with 50% aqueous methanol containing 1% ammonia, the eluate evaporated to dryness under reduced pressure, 0.5 g of p-toluenesulfonic acid added to the remaining pale yellow viscous product oil, and the mixture treated with isopropyl alcohol to give crystals, which are recrystallized from ethanol. Yield 0.82 g. Melting point 131—134°C. $[\alpha]_D^{24}=-29.6°$ (methanol).

Synthesis of Compound 7

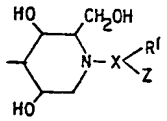
The crude p-hydroxycinnamylmoranoline (1.0 g) previously obtained is dissolved in 30 ml of methanol, 1.0 g of potassium hydroxide added, 2 ml of glycidol then added, and the mixture refluxed for 4 hours. The reaction product is recovered by the procedure for Compound 5 and converted into the p-toluenesulfonate, which is recrystallized from isopropyl alcohol. Yield 0.81 g. Melting point 126—130°C. $[\alpha]_D^{24}=-25.8°$.

Example 23 Synthesis of compound 3

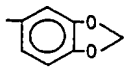
Tetra-O-benzylmoranoline (5.2 g, m.p. 44—46°C, $[\alpha]_D^{24}=38°$ (ethanol) is dissolved in 30 ml of DMF. Anhydrous potassium carbonate (3.0 g) is added, then 3.0 g of the p-methoxyehtoxycinnamyl bromide mentioned in Example 3 added with stirring, and the mixture heated and stirred at 60°—70°C for 6 hours. After the reaction, the reaction mixture is diluted with water, acidified with diluted hydrochloric acid, washed with n-hexane, made alkaline with ammonia and extracted with benzene. The benzene is distilled off and the remaining crystalline substance treated as it is with 50 ml of 24% hydrobromic acid at 90—95°C for 3 hours. The mixture is evaporated to dryness under reduced pressure, and the residue dissolved in water, washed with ether, made alkaline with ammonia and extracted with n-butanol. The extract is purified by silica gel chromatography with chloroform-methanol (3:1) and recrystallized from ethanol. Yield 1.83 g. Melting point 172—174°C $[\alpha]_D^{24}=-48.6°$ (methanol).

CLAIMS

1. Moranoline derivatives of a formula

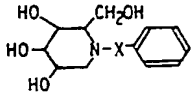


(where X is alkylene which may contain double and/or triple bond(s) therein, R^1 is hydrogen, phenyl or substituted phenyl, and Z is phenyl, substituted phenyl,

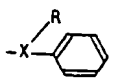


or thienyl) and acid addition salts thereof

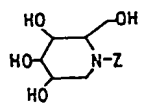
2. N-substituted moranoline derivatives represented by the following general formula and acid addition salts thereof. In the formula, X represents a propylene or propenylene group.



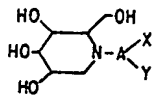
3. An N-substituted moranoline derivative represented by the following general formula. In the formula, Z represents



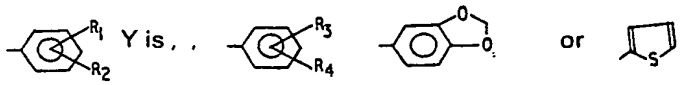
wherein R is hydrogen or phenyl, and X is alkylene or alkenylene containing 4 or 5 carbon atoms when R is hydrogen or X is alkenylene containing 3, 4 or 5 carbon atoms when R is phenyl.



4. An N-substituted derivative of moranoline represented by the following general formula and acid addition salts thereof.

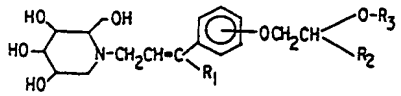


In the formula, A is hydrocarbon residue containing 3—6 carbon atoms and having or lacking a double bond, X is hydrogen, methyl or



wherein R_1, R_2, R_3 and R_4 are the same or different and each is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl, trihalomethyl, phenoxy, dialkylamino, cyano, carboxyl, carbamoyl or carboalkoxy.

5. A substituted cinnamyl-moranoline (following general formula) and acid addition salts thereof.



In the formula R_1 is hydrogen or methyl, R_2 is hydrogen or hydroxymethyl and R_3 is hydrogen, methyl, ethyl or methoxyethyl.

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